

## Review

# Sickle Cell Anemia in Children with Pulmonary Artery Hypertension

Barakat A. Animasahun, MBBS (il), PhD (USA), FWACP (Paed), FMCPaed\*; Moriam O. Lamina, FMCPaed

Department of Paediatrics and Child Health, Lagos State University College of Medicine, 1-5 Oba Akinjobi Road, Ikeja, Nigeria

\*Corresponding author

Barakat A. Animasahun, MBBS (il), PhD (USA), FWACP (Paed), FMCPaed

Department of Paediatrics and Child Health, Lagos State University College of Medicine, 1-5 Oba Akinjobi Road, Ikeja, Nigeria; E-mail: [deoladebo@yahoo.com](mailto:deoladebo@yahoo.com)

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## ABSTRACT

Pulmonary artery hypertension (PAH) ultimately leads to straining of the right ventricle and increases the risk of heart failure in affected patients. Its clinical presentation is similar to that of many other diseases thus delaying the diagnosis until the disease is far advanced. It remains one of the leading causes of death in adults with sickle cell anaemia (SCA) worldwide. It confers a high risk of death with two-year mortality rates as high as 40-50% even at modest elevation of pulmonary artery pressure. Median survival age after detection of the disease is said to be 25.6-months. Early detection of elevated pulmonary artery pressure in childhood and appropriate intervention by optimization of anti-haemolytic therapy may prevent the progression of this complication. The current writes up is a review of literatures on pulmonary artery hypertension among children with sickle cell anaemia. This will give information which will aid early diagnosis and treatment of pulmonary artery hypertension among children with sickle cell anaemia. This will ultimately improve the quality of life of children with sickle cell anaemia and reduce morbidity and mortality from the disease in adults and children living with sickle cell anaemia.

### Keywords

Sickle cell anaemia; Pulmonary artery hypertension; Children.

## INTRODUCTION AND EPIDEMIOLOGY

Pulmonary artery hypertension (PAH) once considered a rare complication of sickle cell disease (SCD) occurs in approximately one-third of adults with SCD.<sup>1,2</sup> Much less is known about its prevalence and natural history in children worldwide.<sup>1,3,4</sup> Pashankar et al<sup>5</sup> conducted the first prospective study in the USA. The study comprised of 75 children all older than six years (mean age range of 9.41-years) and also found a prevalence of 30%. This is similar to the adult findings.<sup>1,2</sup>

Contrary to the study conducted by Pashankar et al,<sup>5</sup> Minniti et al,<sup>6</sup> in another prospective, multicenter study also in the USA conducted a study on 310 SCD patients aged three to twenty years and found a prevalence of 11% (one case seen in a three-year-old patient with SCD) quite similar to that found in another study conducted by Gordeuk et al<sup>7</sup> wherein a prospective longitudinal study of 160 subjects aged three to twenty years, a prevalence of 14.1% was found. They both concluded that the incidence of PAH begins

very early in life (as early as the third year of life) in patients with SCD and increases with age.

However, the result of some small screening studies,<sup>1</sup> a combination of prospective<sup>1,5,8</sup> and retrospective studies,<sup>3,9-13</sup> an aggregation of screening results from over 600 children with SCD in the USA showed a prevalence of 35% nearly identical to 32% in the summarized screening experience in adults with SCD.<sup>1</sup>

In West Africa, where the burden of sickle cell disease is highest, Aliyu et al<sup>14</sup> conducted a subgroup analysis in Zaira, Nigeria, on 208 consecutive SCD patients, aged ten to 52-years in steady-state to determine the prevalence of pulmonary artery hypertension and found a prevalence of 25%. This finding is low compared to the first prospective study conducted by Pashankar et al<sup>5</sup> in the US despite adequate laboratory data showing an increase in hemolysis in subjects in the Nigerian study subjects. The researchers concluded that a relatively lower prevalence found in the study could be due a reduction in the older age bracket (>

35-years) of patients used in the Nigerian study (7%) as compared to (46%) in the US based study. This they attributed to the possibly reduced life expectancy of SCD patients in West Africa compared to the American cohort. In a more recent study, conducted in Nigeria by Dosunmu et al<sup>15</sup> the Lagos State University Teaching hospital (LASUTH), Ikeja, Nigeria on 56 patients with sickle cell anaemia older than 14-years with mean age range (22±6-years) the researchers found a prevalence of 3.6% which is much lower than the US based study. The researchers concluded that the very low prevalence of PAH in subjects studied could be due to the very small sample size used compared to the US based study as well as reduced life expectancy of SCD patients in Nigeria.

Ambrusko et al<sup>11</sup> reviewed out-patient echocardiography of 44 adolescents and found a prevalence of pulmonary hypertension of 26.2%. Qureshi et al<sup>12</sup> did a case comparison of echocardiograms on patients with sickle cell disease and healthy controls and found a prevalence of 16%. However, these studies were retrospective and only eligible patients were recruited thereby introducing bias into their study.

It is obvious from the above that socioeconomic factors may strongly influence the varying prevalence rates of pulmonary artery hypertension worldwide.<sup>16</sup> Even though the prevalence of PAH may increase with age generally in developed countries as seen in the US based studies the contrary maybe for our environment where the life expectancy of patients with SCD is reduced.

### PHYSIOLOGY OF PULMONARY ARTERY PRESSURE

The lungs receive cardiac output with each stroke volume. The pulmonary circulation is normally a high flow, low resistance system that carries blood into the pulmonary microcirculation.<sup>17</sup> Pulmonary artery pressure is a measure of blood pressure found in the pulmonary artery. The normal values for mean pulmonary artery pressure ranges from 8-20 mmHg.<sup>18</sup>

Pulmonary artery hypertension is said to begin when this mean pulmonary artery pressure exceeds 25 mmHg at rest and 30 mmHg during exercise. This definition applies to both adults and children except during infancy.<sup>18,19</sup>

There are other causes of an elevated pulmonary artery pressure some of which are listed below:

- Congenital heart diseases associated increased pulmonary blood flow i.e those with left to right shunting of blood at the atrial, ventricular or great vessel level such as ventricular septal defect, atrial septal defect, atrioventricular septal defect and patent ductus arteriosus.<sup>18,20</sup>
- Pulmonary causes which could be idiopathic as seen in primary pulmonary hypertension. Other pulmonary causes include: Obstructive lung disease such as chronic obstructive pulmonary airway disease (COPD)<sup>15,18,20</sup> and restrictive lung disease such as emphysema.<sup>21</sup> Pneumonia, pulmonary hypoplasia associated with congenital diaphragmatic hernia or

renal dysplasia, peripheral pulmonary stenosis.<sup>18,20</sup>

- Hereditary hemolytic anaemia such as: SCD,<sup>1,5,13,14,18,19,21</sup> Thalassemia,<sup>1,5,16</sup> Hereditary spherocytosis,<sup>5</sup> Paroxysmal nocturnal haemoglobinuria.<sup>5</sup>
- Hepatic disease such as cirrhosis and portal hypertension.<sup>18,20</sup>
- Collagen vascular diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis.<sup>20</sup>
- Granulomatous disease such as sarcoidosis.<sup>20</sup>

### THE PATHOGENESIS OF PULMONARY ARTERY HYPERTENSION IN SICKLE CELL ANAEMIA

The pathogenesis of pulmonary hypertension in sickle cell anaemia (SCA) as suggested by many studies is likely to be multifactorial.<sup>1,5,6,13</sup> Proposed mechanisms include haemolysis-induced endothelial dysfunction<sup>5,14</sup> chronic hypoxemias,<sup>22</sup> asplenia, parenchymal and intravascular sequestration of sickled erythrocytes, iron overload and inflammation.<sup>1</sup>

The role of haemolysis in the development of pulmonary hypertension has been described by many authors.<sup>5,23,24</sup> Haemolysis results in the release of haemoglobin and the enzyme erythrocyte arginase from red blood cells both increasing consumption and decreasing production of nitric oxide (NO). NO is a critical regulator of vasodilatation and vascular homeostasis whose inactivation produces vasoconstriction and proliferative vasculopathy. Minniti et al,<sup>6</sup> in the United States of America found a significant correlation between markers of haemolysis such as lactate dehydrogenase (LDH), aspartate aminotransferase and bilirubin concentration, reticulocyte count suggesting haemolysis plays a strong role in the pathogenesis of pulmonary artery pressure. There was however, no significant relationship found between anaemia and elevated pulmonary artery pressure.<sup>6</sup> This finding was in contrast to that of Pashankar et al<sup>5</sup> where subjects who had elevated pulmonary artery pressure had significantly higher reticulocyte count when compared with unaffected patients. Although, no significant relationship was found between elevated pulmonary artery pressure and some markers of haemolysis (anaemia, bilirubin levels and LDH) was found. In addition, they found that thrombocytosis was significantly associated with elevated pulmonary artery pressure, a finding they attributed to functional asplenia. Hence, they concluded that the pathophysiology of PAH in SCD is most likely multifactorial with haemolysis being just one of the causes in SCD.

Functional asplenia, a clinical condition which occurs in SCA patients, has also been linked to the incidence of pulmonary hypertension.<sup>5</sup> It is speculated that loss of splenic function in patients with SCD increases circulation of platelet-derived mediators, senescent and abnormal erythrocytes in circulation promoting pulmonary microthrombosis and red cell adhesion to endothelium hence leading to PAH.<sup>5</sup>

In Zaira, Nigeria, Aliyu et al<sup>14</sup> found that white blood cell count, platelet count and reticulocyte counts of patients with sickle

cell disease were not significantly associated with an increase in tricuspid regurgitant velocity (TRV) while lactate dehydrogenase was found to have significant associations with an elevated TRV. Hence, they concluded that haemolysis played a major role in the cause of PAH in SCD patients.

This finding in the Aliyu et al<sup>14</sup> study could be attributed to the fact that the subjects recruited for the study were largely those who had been attending regular clinic. Hence, many are treated appropriately and promptly when an infection arises. The above studies show that haemolysis,<sup>5,6,14</sup> a clinical feature seen in patients with SCD, play a strong role in the aetiopathogenesis of PAH among patients with SCD, but beyond haemolysis, other features such as thrombocytosis resulting from functional asplenia seen in them, also play a role.

### CLINICAL PRESENTATION OF PULMONARY ARTERY HYPERTENSION

Pulmonary artery hypertension usually progresses unnoticed.<sup>5</sup> The symptoms of PAH in children are variable with symptomatology depending on the aetiology and severity of disease as well as age of the patient. Symptoms may be nonspecific and may include poor appetite and poor growth in infants while older children may present with nausea, vomiting, lethargy or over syncope.<sup>18</sup> The most common presenting symptom for pulmonary hypertension in SCD is worsening of dyspnoea on exertion.<sup>1</sup> This may wrongly have attributed by clinicians to anaemia and cardiopulmonary evaluation may be delayed. Signs elicited in affected patients include; digital clubbing,<sup>1</sup> On cardiac examination a loud P<sub>2</sub> may be heard an ejection systolic murmur loudest in the pulmonary area also referred to as the Graham Steell murmur,<sup>20</sup> as the disease progresses signs of right-sided heart failure such as an elevated jugular venous pressure (JVP), hepatomegaly, ascites, pedal and peripheral oedema may be seen.

### DIAGNOSIS OF PULMONARY ARTERY HYPERTENSION

The gold standard for determining pulmonary artery pressure (PAP) is by cardiac catheterization. However, this procedure is highly invasive and not suitable for screening purposes.<sup>5,21</sup> Doppler echocardiography is however very sensitive and non-invasive.<sup>4,8</sup> The use of echocardiography to estimate pulmonary artery systolic pressures has been well validated in patients with SCD, and non-invasive assessment correlates well with measurement of pulmonary artery pressures by right heart catheterization.<sup>25,26</sup> An optimal view of TRV is obtained during echocardiography by taking multiple measurements of TRV on multiple views (apical 4 chamber, parasternal short axis, parasternal long axis). An average of these measurements is then taken as the estimated TRV to ensure accuracy. The pulmonary artery systolic pressure is then estimated using the modified Bernoulli equation.<sup>18</sup>

$$\text{PAP} = \text{Mean Right Atrial pressure (a constant of 5 mm Hg)} + \text{Bernoulli derived TRV (4V2)}$$

### MANAGEMENT OF PULMONARY ARTERY HYPERTENSION

It is likely that maximization of standard treatment in patients with SCD particularly targeted at reduction of haemolysis would be beneficial since haemolysis has been found to be a major cause of PAH.

There are currently several Food and Drug Administration (FDA) approved drugs for the treatment of pulmonary hypertension but there are few studies on the efficacy of these drugs.<sup>5</sup> Kato et al<sup>1</sup> reported that the use of phosphodiesterase-5-inhibitor sildenafil reduces pulmonary pressure and improves cardiopulmonary performance in patients with thalassemia and SCD who have already developed pulmonary artery hypertension. This was demonstrated in their study by an increase in the 6-minute walk distance on fifteen patients with SCD who had PAH after. Twelve of the patients were found to have an increase in the 6-minute walk distance after chronic use of sildenafil.<sup>1,27</sup> There are well-documented beneficial effects of therapy with prostanoids (epoprostenol, treprostinil, iloprost, beraprost).<sup>14,28</sup> Endothelin (ET) antagonists (bosentan and sitaxsentan) and possibly phosphodiesterase-5 inhibitors sildenafil in patients with traditional forms of pulmonary arterial hypertension. There are no long-term data on the specific treatment of pulmonary hypertension in SCD and the choice of agents at this juncture is largely empirical.

Hydroxyurea, an antisickling drug which also increases the fetal haemoglobin, is known to help reduce haemolysis but has not been found to significantly impact on the mortality of SCD related pulmonary artery hypertension.<sup>5</sup>

### EFFECT OF SICKLE CELL ANAEMIA ON PULMONARY ARTERY PRESSURE

Sickle cell anaemia is an independent cause of PAH<sup>15</sup> Minniti et al<sup>6</sup> reported that a greater than 2 standard deviation (SD) increase in haemolytic index was associated with a 4.5 fold increase of elevated TRV and an oxygen saturation of  $\leq 98\%$  was associated with a 3.2 fold rise of TRV.

Among patients with SCA who develop pulmonary artery hypertension early in life, it is suspected that between the ages of twenty to fifty years more extensive vascular smooth muscle hyperplasia would have occurred with luminal narrowing that may not respond to therapeutic maneuvers to reduce haemolysis. In advanced cases, irregular, chronically activated endothelium may have accrued *in situ* thrombosis and plexogenic changes that dramatically increase pulmonary vascular resistance. It is speculated that in such advanced stages prevention of haemolysis by transfusion may be ineffective and only pharmacological treatment

can improve pulmonary pressure but gradual progression of the disease is still likely.<sup>5</sup>

### THE EFFECT OF PULMONARY ARTERY PRESSURE ON SICKLE CELL ANAEMIA

Pulmonary artery hypertension has been found to drastically reduce the life expectancy of patients with SCA. Two-year mortality rate is known to be as high as 40-50%.<sup>13,22,23,27</sup>

### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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